Organic & Biomolecular Chemistry

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View Article Online
DOI: 10.1039/C8OB03072C

Journal Name

COMMUNICATION

Palladium-Catalyzed Intermolecular [4 + 2] Formal Cycloaddition with (Z)-3-Iodo Allylic Nucleophiles and Allenamides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Fachao Yan,[‡a] Hanbing Liang,[‡a] Bing Ai,[a] Wenjing Liang,[a] Luyang Jiao,[a] Shuzhi Yao,[a] Pingping Zhao,[b] Qing Liu,*[a] Yunhui Dong,[a] and Hui Liu*[a]

A highly chemo- and regioselective [4 + 2] formal cycloaddition of (*Z*)-3-iodo allylic nucleophiles and allenamides catalyzed by palladium is reported. The methodology proceeds under mild reaction conditions and is tolerant of alkyl , aryl founctional group. The S_N2' substitution at proximal C=C bond performed against Heck or S_N2 pathway, delivered a variety of 2-amino-dihydropyrans and 2-amino-tetrahydropiperidines in moderate to satisfactory yields. The [4 + 2] formal cycloaddition derivatives are convertible to interesting scaffolds 2,6,7,7a-tetrahydropyrano[2,3-b]pyrrole and 2,6,7,7a-tetrahydro-1H-pyrrolo[2,3-b]pyridine derivatives *via* ring-closing metathesis (RCM) with Grubbs catalyst II.

Functionalized 2-amino-dihydropyrans and 2-amino tetrahydropiperidines are prevalen structural motifs, commonly observed in an array of pharmaceuticals and biologically active natural products, such as the representative bioactive moleculers in antitumor, antimalarial, anticancer, treatment of Parkinson's disease, and so on (Figure 1).[1] As a consequence, these important building blocks have received considerable attention in recent years. Their preparation relies mainly on multiple-step synthesis while direct procedures for building these core structures are less explored.[2] Current methods for the construction of dihydropyrans and tetrahydropiperidines scaffolds have been developed through Diels-Alder reaction,[3] Michael addition,[4] Prins cyclization,[5] dehalogenation coupling,[6] cross-coupling domino reaction,[7] dehalogenated carbonylation coupling[8] as well as multicomponent reactions.[9] However, synthetic challenges remains in installing the amino group at 2 position of dihydropyran ring. Due to the importantance bioactivities of these valuable bioactive molecules, the development of new synthetic strategies to functionalized 2-amino-dihydropyrans and 2-amino-tetrahydropiperidines is indispensable.

Recently, our group has demonstrated efficient synthetic methodologies for five- and six-membered heterocycles via transition-metal-catalyzed ring-closing metathesis cyclization.[10] For example, we successfully developed an intermolecular cyclization-Heck reaction of allenamides to access functionalized tetrahydropyridine derivatives, where π-allyl **η¹** and **η³** intermediates were proposed (I, Scheme 1).[11] Allenic scaffold *N*-allenamide has emerged a versatile building block in numerous

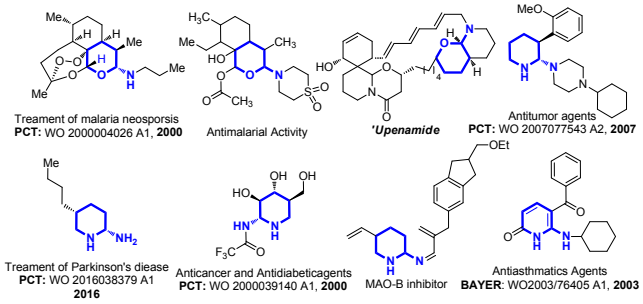
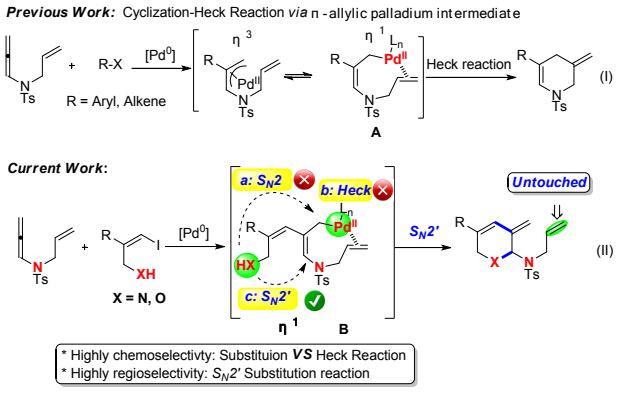


Fig. 1 Biologically-active natural products featuring pyrans and piperidines.



Scheme 1 Previous work and proposal for this work.

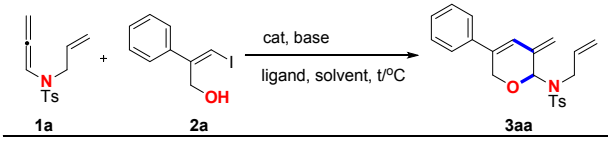
transformations including [m + 2] cycloadditions with suitable synthons.[12] Applying our design to form **η¹** intermediate (**A**), a nucleophilic group was introduced to vinyl iodides that could further react with allenamide to generate the **η¹** intermediate (**B**)

[a] School of Chemistry and Chemical Engineering, Shandong University of Technology, 266 West Xincun Road, Zibo 255049, P. R. China. E-mail: huiliu1030@sdut.edu.cn.
[b] College of Chemical and Environmental Engineering, Shandong University of Science and Technology, 579 Qianwangang Road, Huangdao District, Qingdao, 266590, P.R.China
‡These authors contributed equally to this work.

under palladium(0) catalysis (II, Scheme 1). However, in this case there are many competing reactions pathways: a) S_N2 substitution at distal C=C bond; b) Heck reaction; c) S_N2' substitution at proximal C=C bond. Herein, we would like to report a highly chemo- and regioselective [4 + 2] cycloaddition of *N*-allenamides with (Z)-3 iodide allylic nucleophiles to construct 2-amino-dihydropyran and 2-amino-tetrahydropiperidine derivatives.

In our initial investigations, we tested the reaction of allenamide **1a** with 3-iodo-2-phenyl allylic alcohol **2a** in the presence of 10 mol% $PdCl_2(PPh_3)_2$ and 2.0 equivalents of K_2CO_3 at 80 °C in dioxane under nitrogen atmosphere. To our delight, the reaction progressed with high chemo- and regioselectivity *via* S_N2' substitution way to generate 2-amino-3-methylene-3, 6-dihydro-pyran **3aa** as a single product in 46% yield (Table 1, entry 1). In order to optimize the reaction conditions, we screened other Pd catalysts and commonly used bases and solvents. For instance, we found that the use of $Pd_2(dba)_3/PCy_3$ as catalyst was ineffective (entry 2). We examined the effect of several bases on the reaction, K_2CO_3, K_3PO_4, TEA, and Cy_2NMe in the presence of $Pd(OAc)_2/PPh_3$, and found that that organic bases were better suited compared to inorganic bases (entries 3-6). Dioxane was identified a more efficient solvent compared to MeCN and DMF (entries 6-8). Subsequently, when $Pd(PPh_3)_4$ was applied as catalyst instead of $Pd(OAc)_2/PPh_3$, there was an increase in yield of **3aa** to 70% in dioxane and with Cy_2NMe as base (entry 10). Further optimization of the reaction conditions resulted in $Pd(PPh_3)_4$ (10 mol%) and DMAP (2.0 equiv.) in dioxane at 50 °C, affording the desired product in excellent yield of 97% (entries 11-16). Meanwhile, both catalyst and base were established as necessary inputs for this transformation (entries 17 and 18).

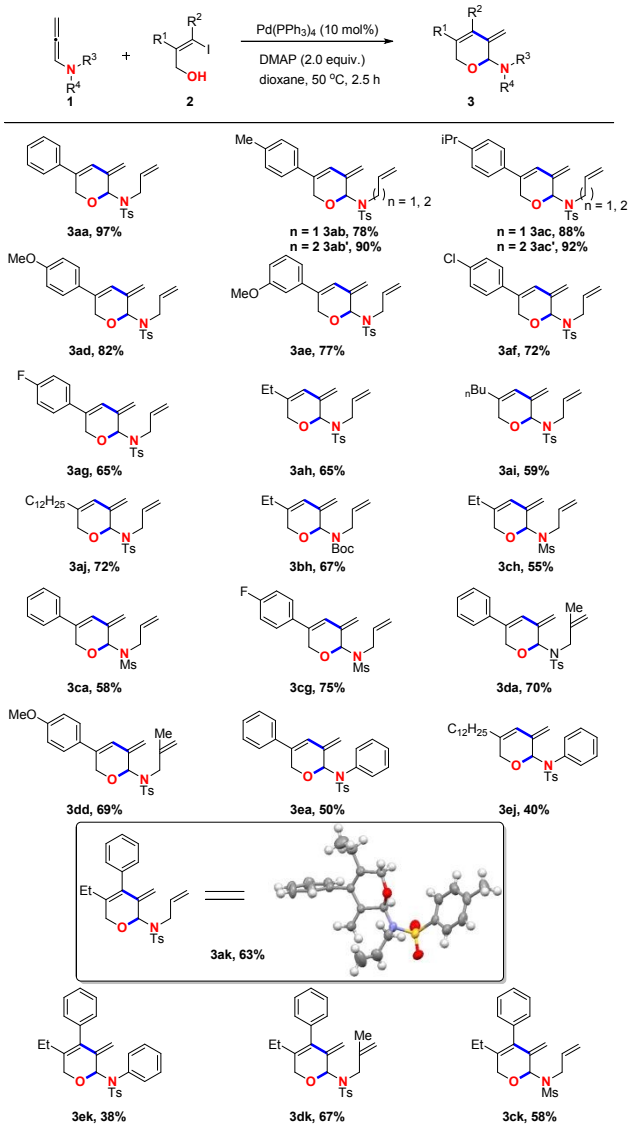
Table 1. Optimization of reaction conditions.[a]



entry	catalyst	ligand	base	solvent	t(°C)	yield (%)[b]
1	$PdCl_2(PPh_3)_2$	-	K_2CO_3	dioxane	80	46
2	$Pd_2(dba)_3$	PCy_3	TEA	dioxane	80	40
3	$Pd(OAc)_2$	PPh_3	Cy_2NMe	dioxane	80	53
4	$Pd(OAc)_2$	PPh_3	K_2CO_3	dioxane	80	5
5	$Pd(OAc)_2$	PPh_3	K_3PO_4	dioxane	80	13
6	$Pd(OAc)_2$	PPh_3	TEA	dioxane	80	62
7	$Pd(OAc)_2$	PPh_3	TEA	MeCN	80	33
8	$Pd(OAc)_2$	PPh_3	TEA	DMF	80	30
9	$Pd(PPh_3)_4$	-	TEA	dioxane	80	58
10	$Pd(PPh_3)_4$	-	Cy_2NMe	dioxane	80	70
11	$Pd(PPh_3)_4$	-	Cy_2NMe	MeCN	80	15
12	$Pd(PPh_3)_4$	-	Cy_2NMe	toluene	80	47
13	$Pd(PPh_3)_4$	-	DIPEA	dioxane	80	53
14	$Pd(PPh_3)_4$	-	DMAP	dioxane	80	79
15	**$Pd(PPh_3)_4$**	**-**	**DMAP**	**dioxane**	**50**	**97**
16	$Pd(PPh_3)_4$	-	DMAP	dioxane	100	69
17	-	-	DMAP	dioxane	80	NR
18	$Pd(PPh_3)_4$	-	-	dioxane	80	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [Pd] (0.02 mmol), base (0.4 mmol), solvent (2.0 mL), N_2, 2.5 h. [b]Isolated yields.

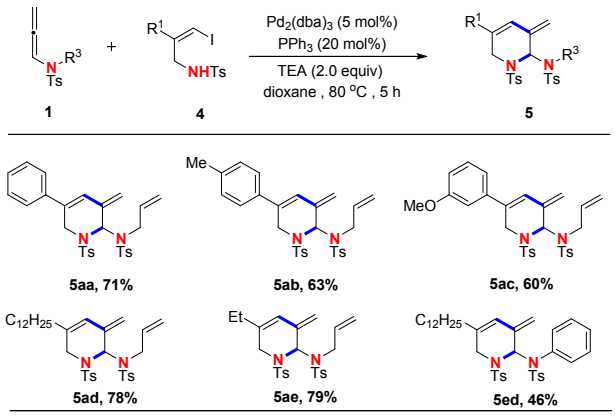
Table 2 Substrate scope of [4 + 2] oxyheterocycles cyclization of allenamides [a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Pd(PPh_3)_4$ (0.02 mmol), DMAP (0.4 mmol), dioxane (2.0 mL), N_2, 2.5 h. [b]Isolated yields.

With the optimized conditions in hand, we embarked testing the substrate scope of this procedure (Table 2). First, we examined the functional groups effect of R^1 substituent of 3-iodo allylic alcohols. The allylic aryl R^1 substituent bearing electron-donating groups (Me, *i*Pr, and OMe) exhibited excellent tolerance in this transformation, delivering the desired products in good to excellent yields (**3aa**-**3ae**). The reactions of substrates with aryl bearing electron-withdrawing halogens provided the 2-amino-dihydropyran derivatives with slightly lower yields (**3af**-**3ag**). While aryl groups at R^1 may engage in conjugation with positive effect for this transformation, the alkyl group allylic substituents at R^1 such as Et, *n*Bu and $C_{12}H_{25}$ have not significantly influence the reaction, affording 2-amino-dihydropyran derivatives in moderate yields (**3ah**-**3aj**). N-protected allenamides with Boc or Ms transformed smoothly to the corresponding

Table 3 Substrate scope of [4 + 2] nitrogen heterocycles cyclization of allenamides



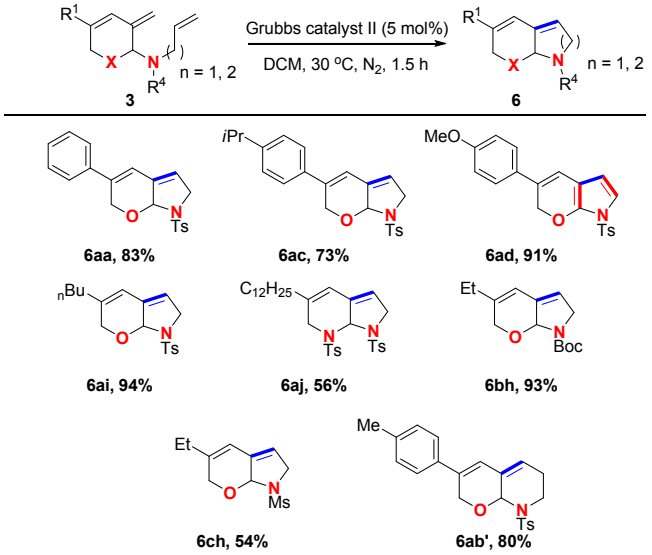
[a]Reaction conditions: **1** (0.3 mmol), **4** (0.2 mmol), $Pd_2(dba)_3$ (0.01 mmol), TEA (0.4 mmol), dioxane (2.0 mL), N_2, 5 h. [b]Isolated yields.

products in good yields (**3bh**, **3ch**, **3ca** and **3cg**). Furthermore, coordinating effects of allylic tether of allenamides were investigated for 2-Me allylic, phenyl and 1-butenyl groups. We found that R^3 substituent, 2-Me allylic group can perform efficiently as well as the allylic group, having corresponding products with homoallylic allenamides obtained in high yields (**3ab'** and **3ac'**). In contrast, the phenyl group substituent impacted by decreased yields for **3ea** and **3ej** under 50% and with the transformation requiring longer reaction time. This result shows that the coordination of the allylic group was essential to this transformation and in accord with our proposed mechanism (The screening of the reaction conditions for the N-phenyl allenamide, see Supporting Information).

Subsequently, the tetrasubstituted vinyl iodides were reacted with N-protected allenamides under standard conditions, delivering the corresponding products in moderate yields (**3ak**, **3dk** and **3ck**). It is noteworthy to mention that a relatively lower yield of 38% was obtained from allenamide substrate-bearing phenyl group, highlighting the importance of the double bond for metal coordination (**3ek**). Despite of the products **3ea**, **3ej**, and **3ek** were produced without allylic double bond, we believe that the π-system of the phenyl may act as a weak ligand for the intermediate transition state. In general, the results confirmed that presence of double bond was a better group for the transformation. We managed to obtain suitable crystals for compound **3ak** and determined the structure by X-ray diffraction analysis (Table 2).[13]

To further explore the substrate scope of this strategy, 3-iodo allylamines were applied instead of 3-iodo vinyl alcohol to prepare 2-amino-3-methylene-1,2,3,6-tetrahydropyridine derivatives (Table 3). After a series of condition screening, optimized conditions were determined as 5 mol% $Pd_2(dba)_3$, 20 mol% PPh_3 and 2.0 equivalents TEA in dioxane at 80 °C for 5 h under nitrogen atmosphere. Meanwhile, We observed that vinyl amine substrate **4** was not completely consumed, presumably because of the lower nucleophilicity of *N*-tosylated amine. Hence, in this instance the substrates ratio of **1a**: **4a** was adjusted to 1.5:1 providing **5aa** in 71% yield. The reaction with both phenyl and alkyl substituted vinyl iodides

Table 4 Applications of the 2-amino-dihydropyrans and 2-amino-piperidines

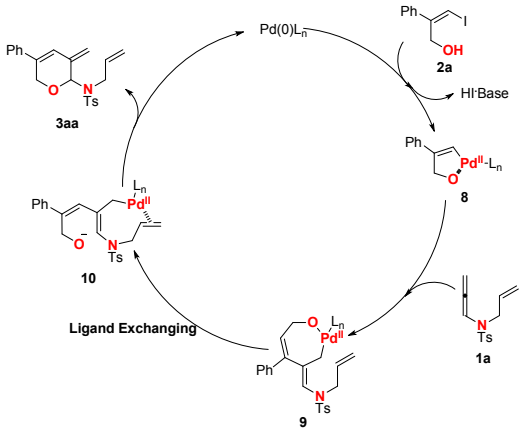


[a]Reaction conditions: **3** (1.0 equiv), Grubbs-II (5 mol%), DCM (1 mL), N_2, 1.5 h. [b]Isolated yields.

delivered tetrahydropyridine derivatives efficiently in good yields (**5ab**-**5ae**). Moreover, phenyl-protected allenamide **1e** can also furnish **5ed** in 46% yield.

To demonstrate the significance of this methodology, the formed 2-amino-dihydropyrans and tetrahydropyridines were converted into 2,6,7,7a-tetrahydropyrano[2,3-b]pyrrole and 2,6,7,7a-tetrahydro-1H-pyrrolo[2,3-b]pyridine derivatives *via* ring-closing metathesis (RCM) using Grubbs catalyst II[14] (Table 4). The 2-amino-3-methylene-3, 6-dihydro-pyran 3aa was subjected to 5 mol% of the Grubbs catalyst II in DCM, at 30 °C for 1.5 h, delivering 3-phenyl-7-tosyl-2,6,7,7a-tetrahydropyrano[2,3-b]pyrrole **6aa** in 83% yield. Subsequently, more examples were examined to generate the corresponding products in good to excellent yields (**6ac**-**6aj**). Notably, the substrate bearing strong electron-donating group OMe can produce the 3-(4-methoxyphenyl)-7-tosyl-2,7-dihydropyrano[2,3-b]pyrrole *via* dehydrogenation and aromatization (**6ad**)[15]. Furthermore, the 5-dodecyl-1,7-ditosyl-2,6,7,7a-tetrahydro-1H-pyrrolo[2,3-b]pyridine **6aj** can also be obtained in 56% yield. Specifically, the boc-protected 2,6,7,7a-tetrahydropyrano[2,3-b]pyrrole **6bh** was obtained in 93% yield. The 2-amino-dihydropyrans bearing homoallylic group can generate 6,7,8,8a-tetrahydro-2H-pyrano[2,3-b]pyridine derivatives **6ab'** in 80% yield. The unique fused heterocyclic molecules are registered for the first time. These compounds are potential candidates for bio-activity testing and therapeutic applications in pharmaceuticals.

According to the above experimental results, we suggest a plausible mechanism of this [4 + 2] transformation as shown in Scheme 2. The reaction is initiated from the oxidative addition of $Pd(PPh_3)_4$ to **2a**, generating the five-membered vinyl palladium complex **8** in the presence of a base.[16] Then, allenamide **1a** is inserted forming a seven-membered ring intermediate **9**. Subsequently, intermediate **9** undergo intramolecular ligand exchange with double bond to form intermediate **10**, releasing the oxygen nucleophile.



Scheme 2 Proposed mechanism.

Finally, product **3aa** is formed through high selectivity proximal S_N2' substitution, with no distal S_N2 substitution at the *N*-allenamides detected. Notably, no Heck-type product was observed, indicating the high chemoselectivity to S_N2' substitution but not insertion to the double bond. According to this transformation, the double bond is not only plays an important role on the ligand exchange, but also easily converted to more valuable molecules.

In summary, we have developed a palladium-catalyzed, highly chemo- and regioselective [4 + 2] formal cycloaddition involving (*Z*)-3-iodo allylic nucleophiles and allenamides. The corresponding products were produced in moderate to good yields. The approach provided a straightforward access to 2-amino-dihydropyrans and 2-amino-tetrahydropiperidines. Moreover, the [4 + 2] formal cycloaddition derivatives underwent an intramolecular ring-closing reaction by means of Grubbs catalyst II. The proposed mechanism confirmed that double bond was essential to the transformation. Further applications of this methodology will be reported in due cause.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Shandong Provincial Natural Science Foundation (ZR2018MB008, ZR2018MB012), National Natural Science Foundation of China (21671121), the CPSF (2016M590736), and the Special Funding for Postdoctoral Innovation Project of Shandong Province (201501002).

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